Ruthless research in a cupboard

Space was at a premium in the early days of molecular biology. The flowering of the science and a new laboratory produced a fertile environment for ideas. Could the same thing happen today?

Francis Crick

THE FINE building the Medical Research Council built for us at the new Addenbrooke's hospital site on the Hills Road was really the outcome of the research that the senior members had done earlier. Fred Sanger had determined the sequence of amino acids in insulin while he was working in the biochemistry department in Tennis Court Road. Max Perutz and John Kendrew's first models of the three-dimensional structure of haemoglobin and myoglobin and our model of the DNA double helix were produced in the Cavendish Laboratory (the physics laboratory), then in Free School Lane.

When I joined the MRC unit in 1949 we were all accommodated in a single room on the top floor of the Austin Wing of the Cavendish. Shortly after that the MRC found more space. Max Perutz and John Kendrew acquired a tiny office of their own. Eventually the unit acquired a further, larger room. There was some discussion as to how we should use this but eventually Max and John decided that Jim Watson and I should have our desks in it ". . . so that you can talk to each other and not disturb the rest of us".

The room got more and more crowded as more desks were moved in. At the time of the DNA model we shared it with Peter Pauling, Jerry Donohue and one or two others. Eventually Cambridge provided a biochemical laboratory on the same floor. Before that I had prepared proteins in the cold rooms of the Low Temperature Station, in the Molteno Institute, or in the chemical room on the top floor of the Austin Wing. This room was intended for metallurgical experiments, not for crystallising proteins. At first there was not even a refrigerator. In those days we filtered suspensions of proteins using suction pumps, connected to the water taps. I caused more than one flood by not fixing the rubber tubing securely enough.

All the time, space was at a premium. When we were negotiating with Sydney Brenner, then in South Africa, he went so far as to write that he would, if necessary, be prepared to work in a cupboard. Eventually we all moved from the Austin Wing to an adjacent hut. Although always a "temporary" building, it still stands, although now it is used only for storing bicycles. Seymour Benzer, Sydney and I shared a minute office (the one to the right of the entrance), while Vernon Ingram occupied much of the limited lab space. A little later, when Mahlon Hoagland was with us, he and I worked for most of a year in Alfred Tissieres's old room in the Molteno Institute. This was not only temporarily vacant when we discovered it, but contained an instrument we had yet to acquire in the unit, a refrigerated centrifuge.

Sydney and I decided to see if we could "acquire" some extra rooms. In those days, before the present mathematical laboratory was built, there was a warren of old buildings on the site. We located a long, thin room that was an annexe to the zoological museum. In the large room next door, the skeleton of a whale hung from the ceiling. The vacant room we had spotted was probably originally used for preparing specimens for the museum. The professor of zoology, Carl Pantin, kindly agreed that we could use it. We did our work on mutant viruses produced by acridine dyes here, but prepared all the Petri dishes and so on in part of another room, just opposite, which we also managed to "borrow". Gunther Stent is fond of saying, when asked if I ever did experiments, that he can testify to it from first-hand experience, since for a time "we shared the same water-bath". Obviously space and equipment were somewhat limited. Given all these makeshift arrangements, it is not surprising that we welcomed the idea of a new and more spacious laboratory.

We did much of our work on a gene in the virus called bacteriophage T4. We made mutants by treating the viruses with many sorts of mutagen, and found that the mutations produced by acridine seemed to occur in different places in the virus's genes from all the others. We suggested that what acridine did was to add a base or delete a base to a gene. This also fitted the idea that acridines slip in between adjacent base pairs of the DNA. The analyses of such mutants was soon to reveal the triplet nature of the genetic code: that is, that a

Francis Crick (right, in 1953): "The pace of research, once we glimpsed its main outlines, was astonishing."

sequence of three bases encodes a particular amino acid in the translated protein.

We were soon able to classify all our mutants as either plus or minus. One can think of the plus mutants as having had an extra base added to the sequence, and the minus mutants as having lost one. We found that all combinations of mutants of like sign (plus with plus or minus with minus) had a mutant phenotype. Almost all those which had a plus combined with a minus had the wild-type phenotype or something rather like it. The key experiment came when we decided to put three mutants of one type together, such as plus-plus-plus. The prediction was that this would have a wild-type phenotype and this turned out to be true.

This was an extremely striking result. Each of the three mutants by themselves showed the mutant phenotype. So did any two of them taken together. But the combination of all three restored the wild-type phenotype. We correctly concluded that this was because it was a triplet code. I remember vividly the evening when we got the results of the decisive experiment. Leslie Barnett and I went in after dinner to examine the plates that had been incubating. One glance at the key plate was enough to show us that the triple plus was wild-type. We carefully checked the plates to make sure we had not got them mixed up. I looked across the room to Leslie and said; "Do you realise, Leslie, that you and I are the only people in the world who know it's a triplet code?"

When the move to Hills Road actually came I was visiting the US again. I had not planned to be away, but the opening of the laboratory had been postponed to a time when I had arranged to be abroad. As far as I could tell, it all went smoothly.

There were two great advantages of the new lab. In the first place we were now in much more intimate contact with Fred Sanger's group. Long before this we had tried to persuade Fred to work with us in the Cavendish, but he was reluctant to leave the biochemistry department for the foreign world of a physics department. We recruited Vernon Ingram instead. After Vernon had shown that sickle-cell haemoglobin differed in only a single amino acid from normal haemoglobin, we had arranged a series of evening tutorial on genetics for Sanger and his colleagues, but this had not led immediately to close collaboration. When the Hills Road lab started we all conscientiously attended all the seminars, hoping that this would draw together the rather different points of view: the structural, the genetic and the biochemical approaches. I decided that a more telling criterion for active collaboration was joint papers. In spite of all the interest and good will, it was several years before these started to appear.

The other advantage of the move was that we could take more visitors. Although we were allowed to have research students, because we were still loosely attached to the university, these we kept to a bare minimum. We preferred to work with post-doctoral students, mainly from the US. By that time the two places in Europe that enterprising postdocs in molecular biology most wanted to visit were the Institut Pasteur in Paris and our new lab in Cambridge, so we had the pick of the crop. They usually stayed for two years, sometimes three. It was attractive to them because they could usually command a good job when they subsequently returned to the US. It was attractive to us because they brought experience gleaned in the other labs, together with willing hands and lively heads to direct them.

As the lab grew it became more difficult to find out what everyone was doing. I suggested two devices to make this easier. An excellent feature of the lab, insisted on by Max

Leading lights, in 1967: from left, John Kendrew and Francis Crick (standing), Hugh Huxley, Max Perutz, Fred Sanger and Sydney Brenner

Perutz, was the canteen on top of the building. This mixed people together in an informal way and was invaluable. After a while, however, I found it disconcerting to have talked to a man for a year or more about his research work and yet not to be able to recall his name. We therefore arranged for everyone, both staff and visitors, to have their photograph taken. These were mounted, with the name written beneath, in the canteen, so that it was easy to discover who was who. Not all the senior staff relished the idea of being identified in this way. I had to get Sydney Brenner's photo by a trick. I got the photographer all set up to take the picture and then engaged Sydney in detailed conversation, unobtrusively leading him to the photographer's chair. No sooner had he sat down than the camera clicked and his face was securely recorded on film.

The other innovation was to hold a set of lectures each year. These took place towards the beginning of the academic year, after most of the new visitors had arrived. The lab lectured to itself for a week, which Perutz wisely restricted to four out of the five days. Nor did we start unduly early, nor go on too late. The talks were mixed. A new staff member might give a broad survey of his previous work. Other talks covered new, exciting developments. A few dealt with plans for future research. All speakers were instructed to talk, not to their close colleagues, but to other members of the lab. Advice sometimes given was to target the talk to Max Perutz, as it was felt that if Max could understand it, we all could!

Sydney and I continued to share an office, but it was now a little larger. I still did a little experimental work, especially after I found that if you wear a white coat and pipette something, people are less likely to interrupt you. Sydney mainly did experiments, so most of the time I had the office to myself. Nevertheless, we usually talked for an hour or so each day. With the rapid development of the subject there was always plenty to discuss. Much of this took place in front of one of our three large blackboards—a scientist is usually quite handicapped in a discussion unless he can scribble on something. Our blackboard even obtained a certain notoriety after John Platt described it in a paper.

Those were exciting days. The genetic code was coming out in the early 1960s. The subject was both confused and moving fast. Our approach was still largely genetic but we did some biochemistry as well. We also put much effort into fractionating and characterising tRNA. I was compelled to write one of my rare reviews of what was going on, entitled appropriately enough, "The recent excitement in the coding problem" (a take-off of the title of an obscure movie). By 1966 the code had finally emerged and we began to cast around for other fields to explore.

The development of molecular biology is too intricate a story to cover here. What was astonishing was the extraordinarily rapid pace of research once we had glimpsed its main outlines. I never thought that there was anything special about this, but recently I have begun to wonder. I think our confidence that these impossible problems might actually be soluble developed a ruthlessness, in both thinking and experiment, which often took us quickly to the heart of the matter. It helped enormously that the MRC, having set us up, let us do what we liked. We did not have to worry, as most people do now, about where our next grant was to come from. We had no need to do the next new but entirely safe experiment. We could ask broad questions and then discuss, at length and in detail, how to blast through to the answers. Too often we were confused, lost in the fog of research, but we kept a clear bearing on the peaks to be scaled ahead of us. The Rockefeller Foundation gave us crucial financial support in the early days, but of the MRC underpinned all our later efforts.

I think there is a useful lesson here. Money for research has to come from somewhere, be it robber barons or the taxpayer. The best way to distribute it is not through some monolithic system, however much care is taken in choosing the right recipients. This is always fallible and can waste scientists' time interminably, sitting on tedious committees. Far better to have many sources of money, with a series of mini-dictators to distribute it. This may be deemed undemocratic but I believe it would work and work well. What I suspect is needed is a prestigious prize for administrators, to be awarded each year or so to the person who has been the most far-sighted and successful in funding research. This would sharpen their minds wonderfully and keep them busily employed distributing the money while we get on with the science. □

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